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Female underrepresentation and higher mortality in AVR remains: Part 2 - TAVR

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Abbreviations:

AS: Aortic stenosis; AVD: Aortic valve disease; AVR: Aortic valve replacement; CABG: Coronary arterial bypass grafting; CAG: Coronary angiography; CMCT: Cardiac multi-slice computed tomography; CPR: Civil Personal Register; CL: Confidence limit; IHD: Ischaemic heart disease; IQR: Interquartile range; ICU: Intensive care unit; LVEF: Left ventricular ejection fraction; OR: Odds-ratio; PCI: Percutaneous coronary intervention; RBC: Red blood cells; TAVR: Transcatheter aortic valve replacement; WDHR: Western Denmark Heart Registry

1. Abstract

1.1. Background: Aortic stenosis is a progressive and degenerative disease, which at some stage needs an aortic valve replacement (AVR). Despite an almost equal prevalence of aortic stenosis, female referral to AVR is lower and unexplained, although partly explained in the differences in risk and outcome. The introduction of transcatheter aortic valve replacement (TAVR) increased the treatment palette of especially of older and high-risk patients. It was suggested that lower female referral would likely change as primary result of TAVR showed survival in women than men.

1.2. Methods and results: Data of 3,863 first time stand-alone TAVR patients from 2007-2020 was obtained from the mandatory West Denmark Heart Registry. TAVR increased from 400 in 2007-2011 to 1648 in 2018-2020, while female fraction declined from 56.0% to 42.7%. Females were older but with significant less comorbidity and generally were found significant differences in most pre-operative parameters between genders. Females more often suffered stroke (3.35 vs 2.19; P=0.035) and bleeding issues (3.01 vs 1.76; P=0.011). The 30-day mortality was higher (3.57 vs 2.81) in females, but both 1- (9.6 vs 11.0) and 5-year mortality (42.5 vs 51.0) was significantly lower in females than men. The mortality in general was high to the very old population undergoing TAVR.

1.3. Conclusion: Female referral for TAVR is substantially less than men and continues to fall. Long-time survival is higher in females. The long-term mortality is improved in females, but female underrepresentation in AVR remains.

2. Introduction

Aortic stenosis (AS), a progressive and degenerative disease is the most frequent valve abnormality [1-2], which at some stage needs an aortic valve replacement (AVR). In younger, low risk patients surgical AVR unquestionably reduces morbidity and mortality [3], while risks and complications have raised some barriers in older and high-risk patients as the crucial parameters of mortality, structural valve deterioration and possible need for a second valve replacement, have some weight when scheduling the patient treatment.

The introduction of transcatheter aortic valve replacement (TAVR) increased the treatment palette of especially older and high-risk patients, as studies showed non-inferior outcome after TAVR compared to surgical AVR (SAVR), and thus indicated a potentially major change in the future handling of AS [4-6].

Significant gender differences have been described in prevalence, treatment, and outcome of especially IHD [7-8], but also of severe AS [2, 4, 6, 9-12]. Aortic stenosis accounts for more than 40 % of valvular diseases and has been reported, although inconclusive, to have an equal prevalence in men and women [6, 11-12], which however is not fully justified with the reported valve replacement ratios. Overall, females seem to be substantially less treated with SAVR compared to men [5-6, 10, 13], although equal [14] or even vice versa [15-16] ratios have been reported. It was suggested that lower female referral rates were likely due to more unfavourable pre-operative baseline characteristics [10] and would likely change in the future, with TAVR showing better survival in women than men [4-5, 11].

Several studies describe higher risk in women scheduled for AVR compared to men [6, 11, 17], originated from higher age and comorbidity i.e., diabetes, hypertension, atrial fibrillation, and anaemia, but opposed to a lower prevalence of ischaemic heart disease (IHD), peripheral arterial disease and renal disease [6,11]. This agrees with the findings that SAVR is commonly used in lower risk patients, and further favouring men [18], as the increased age and comorbidity, might push female patients into higher risk groups.

However, our previous AVR study with huge increase in AVR treatment during the last decade, indicated that TAVR procedures more adds to the total number of patients undergoing AVR, than significantly reduces the number scheduled for SAVR [18]. Further, the impact of the gender specifics in age, risk, and outcome between TAVR and SAVR is not fully explained, and the survival after TAVR compared to the population remains.

3. Materials and Methods

3.1. Data Source

Patients undertaking stand-alone aortic valve surgery from 2000 to 2020 were extracted from the Western Denmark Heart Registry (WDHR), covering approximately 60% of the Danish uptake area. WDHR is mandatory and encompasses detailed patient-, risk-, procedure-, and care related data as well as in-hospital complications of all adult cardiac procedures and is an integral part of clinical practice [19]. Data are collected and registered prospectively, and quality is warranted by validation rules at entry and systematic controls and regular updates. The first TAVR procedures were registered in the surgical database together with other AVR procedures, but in 2015 a dedicated TAVR registry was established within the WHDR, with a great set of extra pre- and post-procedural factors. All data used in this study has been obligatory since 2006.

All patients submitted to TAVR were considered eligible for the study. Patients without valid ID number, incomplete data registration and re-do procedures was excluded from the analysis revealing a cohort of first time TAVR procedures. The study was registered by the Danish Data Protection Agency (1-16-02-230-21 and 1-16-02-455-21). The agency's rules for the use and handling of data were met and written consent is not required for registry-based studies in Denmark.

3.2. Factors and Outcome

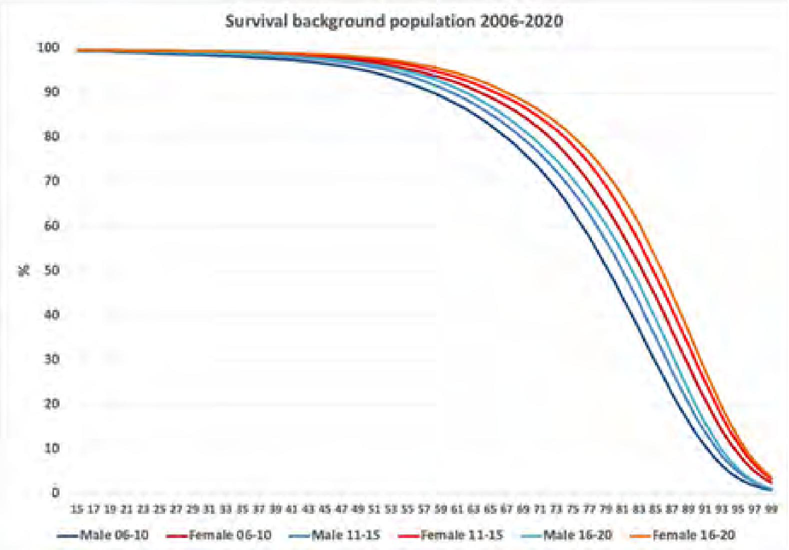
The analysis was centred on gender, age, and comorbidity. The comorbidity score was founded on the EuroSCORE I parameters [20] minus age and gender score and supplemented with points for diabetes treatment (tablet 1 point, insulin 2 points), and was further divided in EuroSCORE patient and cardiac factors where appropriate. In procedures after 2015, the frailty (Dalhousie University Clinical Frailty Scale) was further used as an alternative co-morbidity factor. [21].

The primary outcome was all cause mortality. All Danish citizens have a unique civil personal registration (CPR) number assigned at birth and kept throughout life, enabling cross-linking between different health and civil registries. Data on mortality were obtained daily from this system, which has kept updated records of the entire Danish population regarding vital status, date of death, residence, and migration since 1968.

Additional outcomes were the registered peri-operative complications including stroke, acute myocardial infarction, new dialysis, arrhythmias, valve re-operation within 30-days, severe bleeding/ vessel issues causing surgical intervention or blood transfusion ≥ 6 units and inotrope treatment indicating a complicated postoperative cardiovascular path.

3.3. Background Population Mortality

To compare with background population survival, all patients were individually assigned the predicted risk of death, at the time of the TAVR-procedure. To attenuate the great differences in average living time between men and women, great changes in population survival in especially this older population and the relatively large observation time with steep learning- and improvement curves, all patients were assigned the supposed 1- and 5-year mortality, founded on the official 5-year life tables from Statistics Denmark (Supplement 1) [22]. Thus, with all patients allocated a time, age and gender individual expected mortality, the study groups actual mortality can be analyzed against the background population mortality in a 1:1 ratio in subgroups of selected factors.



Supplement 1: Population background survival, based on 5-year periods and gender. The survival curves are based on one year mortality of the actual ages (15-99 years; Danish Statistics). https://www.dst.dk/en/

3.4. Statistical Analyses

The detailed statistical analysis was primarily based on gender, age, comorbidity, and post-operative complications. Where appropriate, data was gathered in time- and outcome groups. Categorical variables were primarily analysed using the $\chi 2$-test. Depending on data-normality longitudinal data was carried out with Mann-Whitney independent test or independent samples t-test (t-test) together with ANOVA or Kruskal-Wallis for comparisons between parameters, factors and subgroups.

The analysis of outcomes over time was based on Kaplan–Meier survival curves and compared to the individual assigned population mortality. Furthermore, we used model-based Poisson regression analysis, with robust error variance to estimate adjusted risk ratios/odds ratios to identify independent factors with an impact on primary outcome, presented as odds ratios (ORs) with 95% confidence limits (CLs), to identify and evaluate the independent impact of potentially confounding factors. The included covariates were primarily based on age, comorbidity, preoperative surgery and gender. Analyses were performed with MedCalc® software version 20.008 (Mariakerke, Belgium). A probability value of < 0.05 was used to define statistical significance.

4. Results

The WDHR revealed data of 11,290 aortic valve procedures from 2000-2020 of which 3,961 were TAVR. Two patients with non-valid ID preventing follow-up and 16 re-do procedures were excluded together with 70 procedures with missing relevant pre- or postoperative data, leaving an eligible cohort of 3,863 first time TAVI procedures (Table 1).

The overall growth in AVR is shown in Supplement 2. It is observed that, the overall number of AVR has increased by 130% since the introduction of TAVR (2007 to 2020). The analysis of the distribution of TAVR and SAVR shows that, the number of SAVR was highest in 2013 (443), and gradually decreased to 228 procedures in 2020, while TAVR has increased from 220 procedures to 618 procedures in the same period. The analysis of gender distribution in overall AVR revealed that, the fraction of females has decreased constantly since 2000. Additionally, the female fraction in TAVR has also lessened from 56.0% in the first 3-year period to 42.7% in the last 3-year period (Table 2).

The patient characteristics show relatively great differences over time in most registered parameters (Table 2), The fraction of patient with diabetes, reduced left ventricular ejection fraction (LVEF), pre-procedural arrhythmias, FEV1< 80 and no discontinuation anticoagulation medicine was stable in the observation period. The fraction of patients with previous cardiac interventions decreased with 49.7 % for cardiac surgery and 28.7 % for PCI.

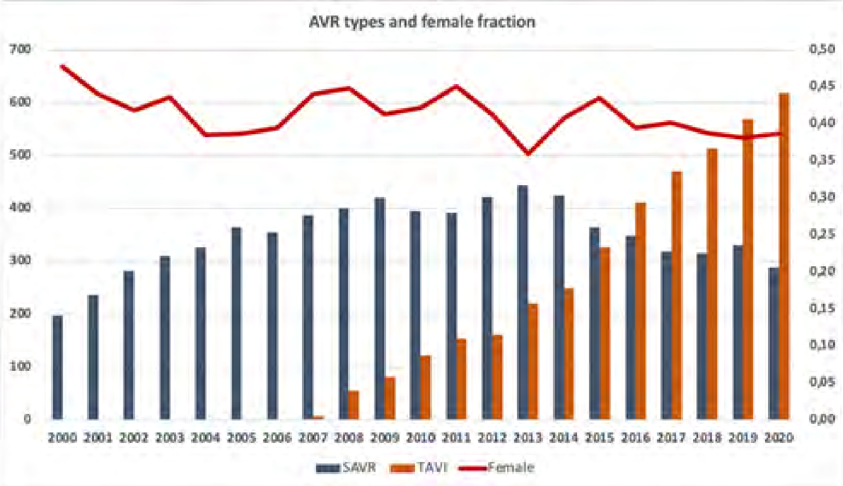
Overall, the risk scores decreased slightly, while the number of patients with higher frailty score increased. Females were two years older than men ($p<0.0001$, t-test), but otherwise showed lower risk with better LVEF, lower comorbidity score, lower fraction of diabetes, lower frequency of arrhythmias together with considerably less previous cardiac interventions (Table 2). The comorbidity score declined significantly during the period ($P<0.001$, ANOVA) and overall females showed a significant lower score than men ($P<0.001$, t-test). This is further outlined in Figure 1, demonstrating that patient- and cardiac risk factors were higher in men, while age factor was higher in females. Despite adding the gender factor, females have higher fractions of low comorbidity and lower fraction of high comorbidity ($P<0.0001$; Figure 2). However, when analysing the frailty score, the picture is less distinct as females overall showed statistically different scores ($P=0.039$) especially in medium range groups from 3 to 7 (Figure 2). The difference in risk factors is further emphasized by 15.9 % fewer women showing FEV_1 less than 0.8 of predicted values compared to men.

Complications after TAVR showed some differences over the time periods. AMI, post-TAVR new dialysis, arrhythmias and inotrope treatment declined, while insertion of a permanent pacemaker after the procedure increased. No differences were found in stroke, re-operation or bleeding issues. Vasoconstrictors declined significantly, primarily beacuse it was used prophylactic in the earlier periods. Females had in general higher frequency of complications although only stroke, bleeding and permanent pacemaker were statistically significant (Table 3).

Mortality decreased substantially from first- (2007-2011) to the last period (2018-2020), with 68.1% in 30-days, 54.3% in 1-year and 19.7% in 5-year mortality (all P<0.0001; χ2-test) (Table 3), while population background mortality only decreased 10-15% in the same period. The raw data showed that females had higher 5- and 10-year survival (Figure 3), although it was not different neither after 30 days nor after one year (Table 3). However, logistic regression analysis with relevant factors did not find difference in mortality between gender. Analysing all mortality 2007-2020 it was 46.4% in men compared to 45.0% in females (P>0.387; χ2-test). Analysing living time after the TAVR, it revealed an average age of 83.0 vs 85.9 years at death, indicating that men lived average 3.00 years and females 3.59 years after the procedure (Table 4, P<0.001; t-test) and the living time after the procedure was generally longer in females independent on age group (Table 5).

Comorbidity, frailty as well as postoperative complications had significant impact on mortality (Figure 4). Regarding comorbidity the 1-year mortality increased from 6.1% to 18.7% and the 5-year mortality from 23.8% to 49.2% as comorbidity score increases from ≤ 1 to ≥ 6. Analysing frailty score, the 1-year mortality increased from 7.1% (frailty 1) to 18.4% (frailty > 5) and the 5-year mortality from 26.2% to 38.8%. The impact of postoperative complication was more pronounced as 30-days mortality increased from 2.0% with no events to 24.4% with more than one event, the 1-year mortality increased from 9.0% no complication to 42.4% and further increasing from 33.8% to 60.6% in 5-year mortality. Only few differences in genders with females showing higher 30-day mortality in association with complications while male showed higher 5-year mortality in relation to frailty socre. No gender differences in relation to comorbidity and mortality.

Both the actual and population background 1- and 5-year mortality decreased during the observation period (Table 3). Besides the small age differences in time periods, the distribution was slightly different with more in youngest groups (< 70 years) increasing from 14.4% to 16.8% and less in the highest groups (≥ 85 years) falling from 29.0% to 25.0%, which combined with the general increased lifetime results in the 15% declined population mortality. The 5-year actual survival compared to the population survival is shown in Figure 5. Both the Kaplan-Meier plot and population background showed statistically higher survival in females compared to males. The difference in population mortality is primarily governed by women's longer living time and secondary the marginal different age group distribution.



Supplement 2: Aortic valve replacement divided on type and year together with female fraction.

Table 1: Cohort of TAVR patients 2007-2020

Procedures	**3.969**
No-Valid ID	-2
Double registrations WDHR	-8
Double procedures	-16
Eligible procedures	*3.943*
Missing pre or post info	-80
Cohort analysis	**3.863**

Table 2: Preoperative demographics and comorbidity divided on periods and gender. FEV=forced expiratory volume; ASA= Acetylsalicylsyre; PCI=Percutaneous cardiac intervention; BMI=Body mass index.

Pre-factor	**2007-2011**	**2012-2014**	**2015-2017**	**2018-2020**	*p-value*	**Male**	**Female**	*p-value*
No	400	630	1185	1648		2100	1763	
Age	81.0± 6.7	80.5± 6.9	80.3± 7.2	80.3± 8.8	*0.026*$^{1)}$	79.5± 7.01	81.5± 6.71	*< 0.0001*$^{\#)}$
Fraction female	56,0	47,8	45,1	42,7	*< 0.0001*$^{*)}$		45,6	
Comorbidity	3.30± 2.70	3.75± 2.93	3,31± 2.82	3.04± 2.71	*< 0.001*$^{1)}$	3.80± 2.96	2.63± 2.42	*< 0.001*$^{\#)}$
Age factor	4.79± 1.31	4.70± 1.39	4.68± 1.39	4.66± 1.34	*0.414*$^{1)}$	4.51± 1.39	4.90± 1.29	*< 0.001*$^{\#)}$
EuroSCORE 1 + DM	8.66± 2.53	8.93± 2.90	8.44± 2.82	8.12± 2.80	*< 0.001*$^{1)}$	8.31± 3.00	8.53± 2.56	< 0.001$^{\#)}$
FEV1 < 80% predict			47,7	46,4	*0.495*$^{*)}$	50,3	42,3	*0.0004*$^{*)}$
Frailty 0-1			2,96	3,64	*< 0.0001*$^{*)}$	4,50	2,51	*0.039*$^{*)}$
Frailty 2-4			68,77	61,19		61,40	60,90	
Frailty 5-6			23,40	28,79		27,46	30,55	
Frailty > 6			4,88	6,37		6,64	6,03	
No diabetes	83,50	84,13	83,04	80,95	*0.501*$^{*)}$	79,81	85,42	*<0.0001*$^{*)}$
Diabetes tablet	9,50	9,21	10,30	11,47		12,00	8,79	
Diabetes Insulin	6,00	6,51	6,58	7,52		8,05	5,56	
Ejection Fraction	50,7	49,8	50,2	50,4	*0.701*$^{*)}$	48,0	53,0	*< 0.001*$^{*)}$
Pre-arrhythmias	25,8	31,0	30,8	28,6	*0.206*$^{*)}$	33,2	24,8	*<0.0001*$^{*)}$
Non-paused ASA	45,0	43,3	49,6	62,1	*<0.0001*	53,9	53,0	*0.537*$^{*)}$
History cardiac surgery	29,8	26,5	15,9	15,0	*<0.0001*$^{*)}$	24,5	11,7	*<0.0001*$^{*)}$
History PCI	34,8	31,0	29,2	24,8	*<0.0001*$^{*)}$	34,0	21,2	*<0.0001*$^{*)}$
BMI< 18.5	3,79	2,93	1,91	1,23	*< 0.001*$^{*)}$	0,64	3,57	*0.0001*$^{*)}$
BMI 18.5-24.9	41,73	39,51	38,09	35,84		33,50	42,75	
BMI25.0-29.9	39,30	35,93	38,00	38,00		42,98	31,58	
BMI 30.0-34.9	11,11	15,12	16,26	17,33		17,16	14,68	
BMI 35.0-39.9	3,52	5,53	4,00	5,31		4,35	5,26	
BMI ≥ 40.0	0,54	0,98	1,74	2,28		1,37	2,16	

Statistics: $^{*)}$ χ2-test; $^{1)}$ ANOVA, $^{\#)}$ Independent t-test

Table 3: Mortality and postoperative complication divided on observation periods and gender. RBC=red blood cells; PM=pacemaker; AFLI=atrial fibrillation; VT/VF=ventricular tachycardia/fibrillation. Statistics: χ2-test.

Mortality	**2007-2011**	**2012-2014**	**2015-2017**	**2018-2020**	*p-value*	**Male**	**Female**	*p-value*
Number	400	630	1185	1648		2100	1763	
Actual 30 days	7,25	3,97	2,53	2,31	< 0.0001	2,81	3,57	0.176
Actual 1-year	17,25	13,17	9,96	7,89	< 0.0001	11,00	9,59	0.151
Population 1-year	6,98	6,54	6,10	5,91	< 0.0001	6,54	5,75	< 0.001
Actual 5-year	52,00	50,48	41,75		0.0003	51,03	42,47	0.0002
Population 5-year	34,62	32,79	31,71		< 0.001	33,50	31,82	0.024
Complication								
Redo within 30 days	1,50	0,63	0,76	0,73	0.422	0,71	0,91	0.503
Stroke	4,00	1,90	3,38	2,25	0.071	2,19	3,35	0.035
Myocardial infarction	5,00	2,38	0,84	0,85	0.032	1,19	1,93	0.666
New dialysis	2,75	1,27	1,10	0,61	0.003	1,10	1,08	0.962

Vasoconstrictors	60,25	49,68	37,55	18,45	< 0.0001	32,43	35,28	0.059
Inotropes	16,75	11,75	5,82	3,28	< 0.0001	7,24	6,35	0.281
RBC ≥ 6 units	3,75	1,59	1,35	0,55	0.398	0,95	1,70	0.157
Bleeding issue	3,00	1,90	2,28	2,37	0.721	1,76	3,01	0.011
Permanent PM			7,85	10,74	< 0.0001	7,76	6,07	<0.001
None	72,75	74,60	79,83	81,80	< 0.0001	78,62	79,64	0.473
AFLI	15,25	15,40	8,86	6,13		9,38	9,47	
BLOCK	7,50	7,62	9,11	10,25		9,38	8,96	
Other	2,50	1,59	1,52	1,21		1,67	1,30	
VT/VF	1,75	0,63	0,42	0,55		1,09	0,50	
Postoperative event	14,75	8,41	7,59	6,74	< 0.0001	7,05	9,36	0.009

Table 4: Number, average age and survival time divided on age groups and gender. No difference between age groups (P=0.244) or gender (P=0.626) (2-way ANOVA) but analysing overall figures the survival is longer in females (P<0.001; independent sample t-test).

Age group	No	Average age Male		No	Average age Female		Survival Years	
		Procedure	Death		Procedure	Death	Male	Female
<60.0	10	55,90	58,27	4	43,00	47,00	2,37	4,00
60.0-64.9	24	62,71	64,89	5	63,00	65,84	2,18	2,84
65.0-69.9	46	67,35	70,66	25	67,52	70,73	3,31	3,21
70.0-74.9	109	72,42	75,08	49	72,39	76,01	2,66	3,62
75.0-79.9	224	77,29	80,13	130	77,17	80,44	2,84	3,27
80.0-84.9	295	81,96	85,15	284	82,22	86,03	3,19	3,81
85.0-89.9	207	86,75	90,04	213	86,88	90,40	3,29	3,52
≥ 90.0	60	91,12	93,67	84	91,71	95,36	2,55	3,64
All	**975**	**79,97**	**82,98**	**794**	**82,26**	**85,85**	**3,00**	**3,59**

Table 5: Logistic regression analysis of impact of relevant factors and mortality

Factor	1-year	10-year
Age score	1.06 (0.98-1.15)	1.21 (1.15-1.27)
Comorbidity score	1.20 (1.15-1.25)	1.16 (1.13-1.19)
Pre surgery/PCI	0.82 (0.64-1.04)	1.15 (0.99-1.34)
Gender	1.26 (0.82-1.28)	1.07 (0.93-1.22)

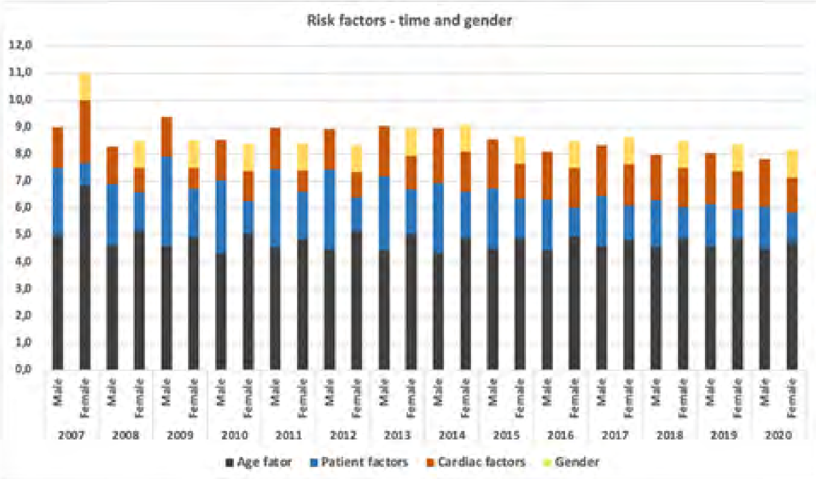


Figure 1: Risk factors divided on years and gender. The risk factor groups are: age, patient, cardiac and gender. Totals, patient, and cardiac factors was significant different (P< 0.001) over years. No difference in age factor (P=0.673). Significant difference (P<0.001) between men and women in patient 2.01 vs 1.29, cardiac 1.78 vs 1.32, age 4.51 vs 4.90. (statistics 2-way ANOVA).

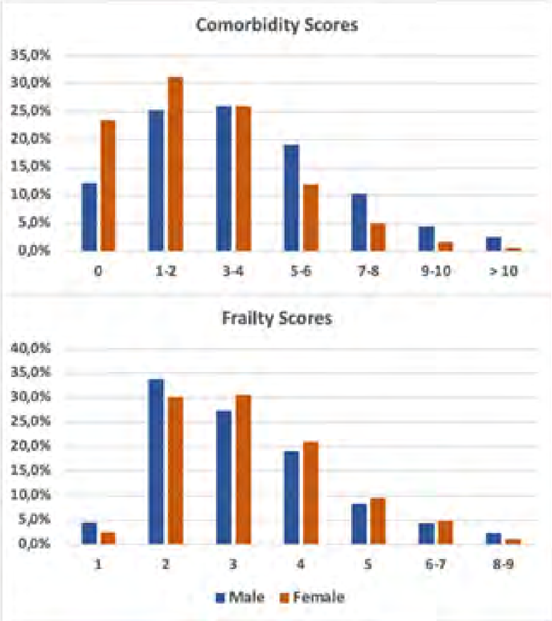


Figure 2: Group percentages of comorbidity score (upper panel) and frailty score (lower panel) divided on gender. Both scores are statistically significant. (Comorbidity P<0.0001 and frailty 0.039; 2-test).

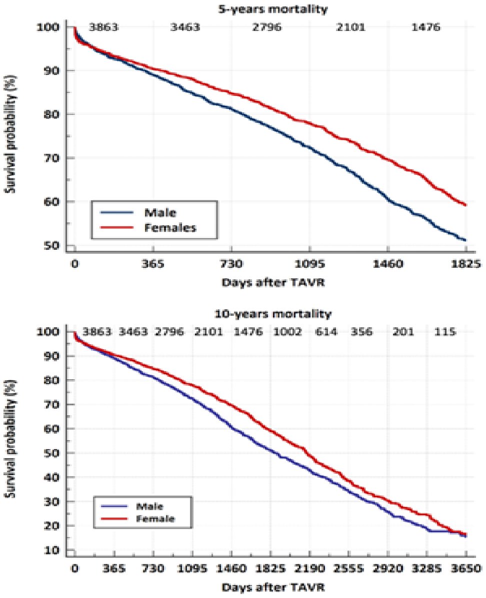


Figure 3: 5-year (upper) and 10-years Kaplan-Meier survival plot divided on gender (5-years OR females 1.29 (1.16-1.43); P<0.0001); 10-years OR females 1.21 (1.10-1.33); P<0.0001)

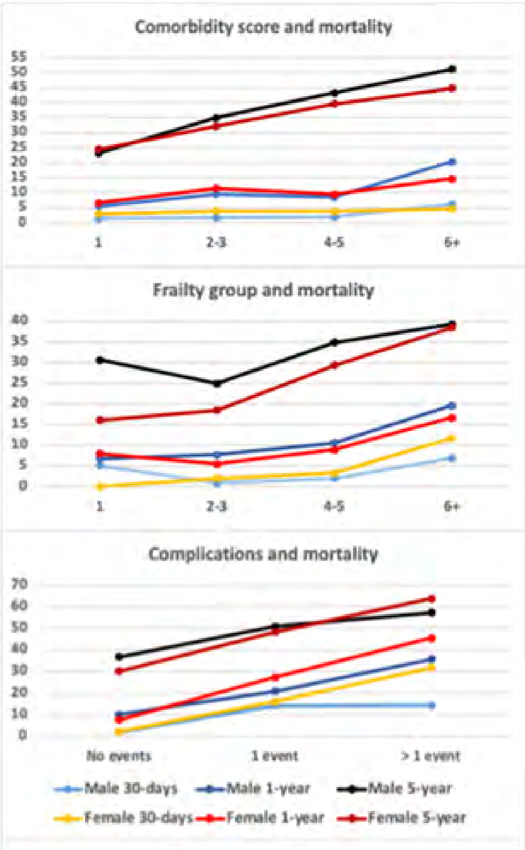


Figure 4: Association between mortality and comorbidity score (upper panel), frailty group (middle panel) and post procedural complications (lower panel) and gender. Mortality increases with comorbidity score (P<0.001) with no difference in gender in 30-days (P=0.096), neither 1-year (P=0.657) nor 5-year (P=0.070). Frailty, difference in all score groups (P<0.001), while no difference between gender in 30-days (P=0.636) and 1-year mortality (P=0.509), but males higher in 5-year mortality (P=0.043). Complications, mortality difference between event groups (P<0.001) and higher in females after 30-days (P=0.002), while no difference between gender in 1-year (P=0.218) and 5-year (P=0.879).

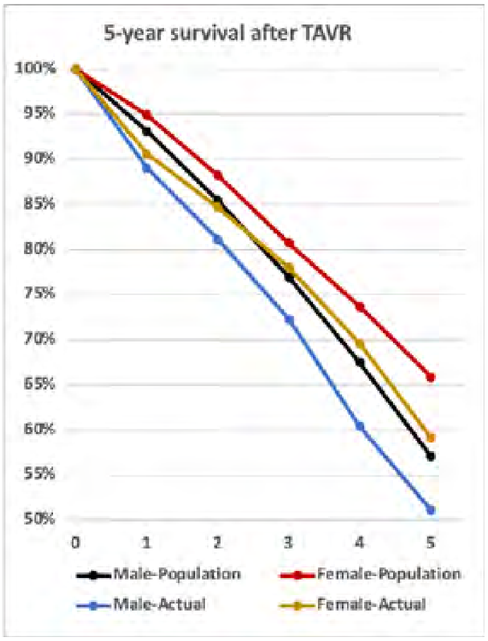


Figure 5: Actual and population 5-year survival. Neither men nor women actual survival approached the population survival in the 5 years period. Both Kaplan-Meier survival plot ($P<0.001$) and the background population showed statistically significant difference between genders ($P<0.001$).

5. Discussion

In this large multicentre study, females are treated less often with TAVR than men and was further underlined by a decline in the female/men ratio during the last decade. As the age of the TAVR patients is stable during the whole period and the number of SAVR procedures in the same geographical uptake area has declined, one could speculate that the oldest SAVR patients, especially men, were pushed into the TAVR group with the result of enhanced female under representation.

The previous findings decline in the female fraction in SAVR might be substantiated with the assumptions that TAVR was preferred to avoid the higher risk of patient prosthesis mismatch, postoperative complications and mortality observed after SAVR [2, 5, 10,11,18, 23]. As earlier reports showed better survival in females [4-6,11] one would expect a shift towards TAVR and a compensatory rise in fraction of females in TAVR. However, as the female fraction also declined in SAVR [18], the overall result, despite a more than 200% increase in referrals from first to last period, a moderate fall in female fraction appears prominent as male fraction increased almost twice that of females.

Increasing rates of AVD are highly correlated with increasing age. Further an added rise is seen in Western countries [24], secondary to corresponding rise in elderly population, following a higher rise in AVR procedures [25]. Interestingly, we found this high increase in TAVR procedures, without notifying differences in patient age.

The initial appeal of TAVR was the possibility of offering a treatment in inoperable and high-risk patients, which was associated with reduced procedural morbidity and reduced short-term mortality compared to SAVR, prompting the wide spread of TAVR [26]. The findings in PARTNER 3 show similar results in low-risk patients [27]. Additionally, the raise in the proportion of patients discharged directly to home and the shorter length of stay can be interpreted as proxy of a general improvement of perioperative care that translates into better morbidity and mortality over time with further logistic advantage, increased cardiovascular surveillance and robust efforts of secondary prevention [28-29], may have stimulated TAVR rise in Denmark.

Further, there is no doubt that females have different clinical presentations, pathophysiology, and valvular calcification of AS [9-11, 30] and demonstrate specific clinical and pathophysiological features in myocardial adaptation following AVR. This results in more hypertrophic hearts, with relatively thicker ventricular walls and smaller end-diastolic diameters [31-32], which further can be enhanced by the modulating impact of oestrogens [33]. The discrepancies in the numbers raise some questions and a previous study concluded that women with AS were less likely to be seen by a specialist and less likely to be referred for testing [13], which hardly should be the case in our health care system with free and uniform health surveillance and treatment. Looking into the WDHR data of 13,827 first time CAG or CMCT from 2006 to 2020 with the indication of aortic valve or aortic disease indication 40.6% were females and from this cohort, somewhat fewer women (78.5% vs 82.55%; $P<0.0001$, 2-test) were referred to surgical/transcatheter treatment. Although not all CAG/CMCT are for AVR (aortic/mitral approximately 6:1 in the surgery registry) the total AVR treatment indicate that the small difference in referral to AVR treatment cannot account the overall difference in numbers of treatments. As the female ratio has continued to decline despite the huge increase in TAVR the findings support some barriers in both pre- and in-hospital handling of females with the majority declined for investigation and never presented to the hospital system.

Some of the reasons for simultaneous decline in fraction of females in TAVR can be speculated as, differential local indications for TAVR based on age, comorbidities along with cost considerations, personnel skills, equipment availability. With a uniform medical training and government funded health system in Denmark, cost, skills, and equipment availability may not be the reason for simultaneous decline in female fraction in TAVR. Further, patient preference or consent play major role in the decision making as based on the obligatory information about postoperative complications such as bleeding and stroke provided during consultation, patients may opt for time tested SAVR.

In agreement with previous studies [10, 17, 33] females in the AVR population are older, although the 2-years difference at time of procedure in our study is less pronounced. Likewise, females have lower comorbidity, like less pre-existing cardiovascular risk factors and diabetes [6,10-11, 33]. Further, women undergoing AVR have less fibrosis than males assessed by perioperative myocardial biopsy analysis [33] and cardiac magnetic resonance imaging [35] and thus confirm that there are important differences in the physiological adaptation to the hemodynamic burden of AS. All these differences together may facilitate the enhanced survival found in women after TAVR in earlier studies. Thus, despite being older, women have fewer comorbidities and better medium to long-term survival after transcatheter intervention [4-5, 11, 30, 33, 36]. The higher age at procedure time may partly be explained by females being older. Some have found that females account up to 70% of patients diagnosed with AS in the group older than 80 years of age [37], which however, is somewhat higher than in our study where only 51% of patients above 80 years of age is females.

Worldwide, the number of TAVR has doubled in the last five years [38-39], but the increase has been even greater in our uptake-area with an increase of 133% (2011-15 vs. 2016-2020). However, this has not changed the lower and falling female ratio and strongly disagree with reports stating that female fraction is 50-60% of TAVR [36, 40-42].

Complications after TAVR were less frequent in our study than reported in the earlier papers [30, 42-44]. However, we found higher frequency of bleeding issues and stroke in females. Both the short- and long-term mortality in our study is substantially lower than earlier reports [30. 36, 44] which partly can cloud the difference in mortality in our study. The raw data showed a lower long-term mortality in females. Nevertheless, the difference disappears when attenuating with relevant factors in logistic regression analysis as females have less risk factors. Further, in this elderly patient group with the age close to the average Danish population living age, at the time of intervention, may also have impact on mortality. One can further speculate that the lower risk factors play major role in the selection process allowing less females scheduled for investigation and treatment of AS.

5.1. Strengths and Limitations

The authors had full access to all investigational and procedure related data registered in the WDHR and declare accountability for the data integrity and analysis.

The primary strengths of this study are the use of mandatory and obligatory prospectively reported data from all the institutions in a well-established uptake area. The large cohort with detailed and complete follow-up data on all patients undergoing all types of cardiac interventions during more than two decades allows robust estimations of patients, results, and adverse events in patients scheduled for SAVR and TAVR.

However, the retrospective nature of study data carries possible intrinsic bias and conveys possible confounders, but the mandatory registration and all included patients and outcomes can be accounted for, attenuate this issue. Nevertheless, our study has inherent limitations, as we cannot exclude possible effects of missing covariates, which potentially increase the risk of confounding. Both preoperative evaluation, indications and clinical practice and policies have changed slightly over the observation time, but the treatment in Denmark is generally very uniform, and due to the education system, all doctors are trained in more than one centre.

6. Conclusion

The number of females referred for AVR is far less than men and has not increased after introduction of TAVR. Although more complications and equal short-term mortality females in we found some indications of the lower long-term mortality, although attenuated by risk factors and the elderly patient group undergoing TAVR.

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